The Activated Coagulation Time of Whole Blood as a Routine Pre-Operative Screening Test

PAUL G. HATTERSLEY, M.D., *Sacramento*

■ *Patients with disorders of hemostasis who undergo surgical procedures are in danger of hemorrhage. While the careful medical history remains the most sensitive test of a bleeding tendency, some such patients can give no suggestive history. In three patients with coagulopathy—one with mild classical hemophilia, one with Christmas disease, and one with warfarin toxicity—the abnormality was missed by routine preoperative history but promptly detected by the routine preoperative use of the activated coagulation time* (ACT). *Either this test or the activated partial thromboplastin time should be included in the routine preoperative work-up, along with appropriate additional tests of the hemostatic mechanism.*

PROBABLY VERY NEARLY one person in a thousand has a congenital disorder of the hemostatic mechanism. The minority of them have obviously severe coagulopathic conditions, their histories replete with bleeding episodes. Many more of them have milder disorders. Some can give no personal or family history of abnormal bleeding. Yet all of these persons, as well as the many with acquired hemostatic disorders, are in some hazard if they undergo an operation without recognition and appropriate handling of their disordered hemostasis.

A simple preoperative study should uncover the vast majority of these potential bleeders. Yet routine preoperative laboratory screening for bleeders has fallen into wide disrepute. Much of this disrepute doubtless stems from the well-established insensitivity of the Lee-White coagulation time, which for many years was everyone's routine screening method. Many physicians do not recognize that, without downgrading the importance of the careful preoperative history, modern medicine can now offer much more sensitive and reliable tests of the hemostatic mechanism, and can perform them at relatively little expense in time and materials.

This paper will report upon three patients with potentially dangerous coagulopathic conditions which were missed completely by preoperative history, and were immediately detected by bedside use of a routine activated coagulation time of whole blood (ACT).

The Activated Coagulation Time (ACT)

The author originally modeled the activated coagulation time of whole blood (ACT)[1] after the activated plasma recalcification and partial thromboplastin time techniques of a number of workers. It is a simple bedside test in which whole blood is massively contact activated by drawing it directly onto diatomaceous earth. We found a mean clotting time, when observed at 37° C, of 1 minute and 47 seconds (1'47"). The times in five thousand normal subjects presented a very acceptable bell-shaped curve of

From the Sacramento Medical Center, University of California, Davis, School of Medicine.

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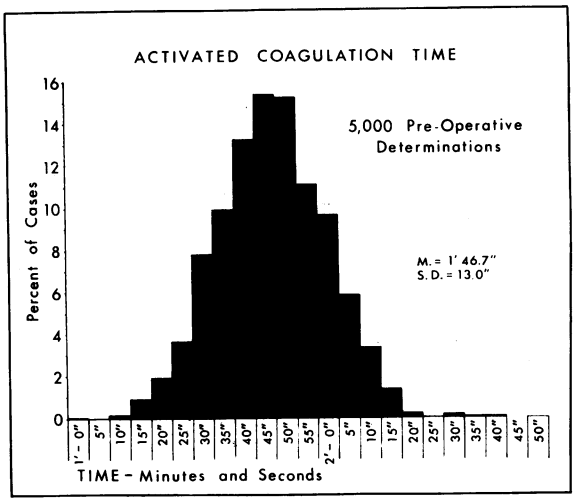
Reprint requests to: Sacramento Medical Center, 2315 Stockton Boulevard, Sacramento, Ca. 95817 (Dr. P. G. Hattersley).



distribution (see chart). The standard deviation in this group was 13 seconds, giving a 95 percent range (Mean ± two standard deviations) of 1 minute and 21 seconds (1'21") to 2 minutes and 13 seconds (2'13"). We found the test quite precise and reproducible, with a coefficient of variation, on duplicate determinations, of 4.5 percent in the normal range.

We at that time reported the ACT sensitive to factor VIII (AHG) deficiencies up to 25 percent of normal, whether due to classical hemophilia or von Willebrand's disease, but somewhat less sensitive to factor IX (PTC) deficiency. We had found it very sensitive to deficiency of factor XII (Hageman), and it had readily detected severe depression of vitamin K-dependent factors in patients receiving hypoprothrombinemic drugs, and in those with severe liver disfunction. It had on a number of occasions demonstrated the coagulation defect of intravascular defibrination syndrome, and had proven a valuable and time-saving substitute for the Lee-White test in the control of heparin therapy. We have also used it extensively in the control of anti-hemophilic therapy.[2]

Since its original description, tens of thousands of these tests have been performed in many centers, the normal values remaining unchanged. Djerassi,[3] in a personal communication, reported detecting factor XI (PTA) deficiency with a modification of this test, and Brittin[4] similarly described a patient with isolated deficiency of factor X (Stuart-Prower factor), which the ACT readily demonstrated. The test has likewise proven very sensitive to deficiency of the Fletcher factor.[5] Our own experience[6] indicates that it will not detect the moderate fibrinogen deficiency of heterozygous fibrinogenopenia, although the characteristic soft clot after retraction suggests the diagnosis. We as yet have no information regarding the sensitivity of the ACT to the rare single deficiencies of factors V (proaccelerin) or VII (proconvertin), or of prothrombin.

Methods

In performing the ACT, we have followed exactly the technique originally described,[1] drawing 2 mm of blood by the second tube technique into a warm, evacuated tube containing 12 mg of diatomaceous earth*, incubating the tube at 37° C in a heat block or small vacuum bottle, tipping it each five seconds after the first minute, and recording the time of appearance of the first definite clot. Times over 2'10" we have considered presumptively abnormal, indicating need for further study of the blood and the patient. We have usually performed the test in duplicate; and technologists, technologist trainees, nurses, medical students and interns, after a minimum of experience, have encountered little difficulty in reading the end-point or in obtaining good agreement between their paired observations.

With the ACT in preoperative screening, we have routinely determined the bleeding time by the Duke method,[7] to detect those disorders of hemostasis not related to defects of the intrinsic coagulation cascade. We have also scanned a stained blood smear for adequacy of platelets, and have observed the ACT tube after overnight incubation at 37° C, to evaluate clot retraction and fibrinolysis. We have considered this a minimal screening series for hemostatic disorders in preoperative patients.

When we have encountered a prolonged ACT in a preoperative patient, we have followed it with further investigation. For such studies we have drawn nine volumes of venous blood into one volume of 0.1 Molar acid citrate** solution in a plastic tube. We have used the one-stage prothrombin time (PT) of Quick;[8] the "P & P" test of Ware and Stragnell;[9] the thrombin time

*Celite (TM), Johns Manville Co. Evacuated tubes available from Becton-Dickinson and Co., Tube #3206 XF136.

**Mixture of three parts of 0.1 M Sodium citrate and two parts of 0.1 M citric acid.

(TT) as described by Hardisty and Ingram;[10] the quantitative fibrinogen technique of Cullen and Van Slyke;[11] and the kaolin activated partial thromboplastin time (PTT) of Proctor and Rapaport.[12] For further diagnostic tests we have used the PTT and PT techniques on equal mixtures of patient's plasma with normal plasma, with citrated plasma of patients with known severe coagulation defects, or with artificially prepared deficient plasmas. In selected cases we have performed single factor assays, or sent plasma specimens to referral coagulationists for such tests.

Case 1—Mild classical hemophilia with intracranial hemorrhage

A 20-year-old college basketball player entered the hospital because of confusion, headaches, nausea and vomiting, all coming on shortly after a heavy fall. Reliable history proved impossible because the patient was in a semi-stuporous state and his family lived in another city. Under observation, signs of increasing intracranial pressure developed, with incoordination of the left arm and leg, and nystagmus. The neurosurgeon considered craniotomy.

On routine preoperative study, we found the bleeding time, platelets and clot retraction normal, but the ACT definitely prolonged (2'55", 3'00). We also found a prolonged PTT (64 seconds), corrected by mixture of his plasma with an equal volume of plasmas severely deficient in factors IX, XI and XII, but not by plasma deficient in factor VIII. The factor VIII assay, performed for us elsewhere,* was 11 percent of mean normal. We immediately infused eleven units of cryoprecipitates, as prepared by the technique of Pool and Shannon.[13,14] (One unit = precipitates from 450 ml of donor blood). A few minutes later we found the ACT mid-normal (1'40"), further supporting our diagnosis of mild classical hemophilia.

The patient subsequently received eight units of cryoprecipitates each eight hours for 10 days. His ACT remained normal during this period, although his plasma fibrinogen rose to 850 mg per 100 ml, presumably due to the large amount of fibrinogen in cryoprecipitates. (See Hattersley and Dimick.[5])

Signs of intracranial pressure gradually subsided, making surgical interference unnecessary, and the patient left the hospital four weeks after admission, with only mild residual neurological signs. Six months later he returned to college, apparently completely well. At that time we found an ACT of 3'10" and an activated PTT of 64.6 seconds, essentially the same as before treatment.

The parents, when finally contacted, said that the boy had been considered a "bleeder" as a child, and that two maternal uncles had likewise had bleeding problems. They had withheld this information from him.

Case 2—Mild "Christmas disease" with minor operation

An 11-year-old boy entered the hospital for removal of a small angioma from the anterior chest wall. The mother, in response to questioning by the surgeon, denied that the boy had ever bled abnormally, although he had had teeth extracted. Routine pre-surgical tests showed a normal bleeding time, clot retraction and platelets, but a slightly prolonged ACT in duplicate (2'45", 2'35"). Further investigation showed a normal Quick prothrombin time and thrombin time, but a somewhat prolonged PTT (53.5 seconds), corrected by an equal mixture with plasma deficient in factor VIII, but not by factor IX deficient plasma. We subsequently obtained a factor IX assay of 6.3 percent,** confirming our impression of mild Christmas disease.

The surgeon cancelled the elective procedure and carefully re-questioned the patient's mother, who eventually admitted that the boy had on two occasions bled badly following tooth extractions, and once following a scalp laceration. She had purposely withheld this information for fear that it would prevent the operation on her son.

On readmission of the patient, the ACT remained prolonged at 2'45" and 3'00", but infusion of 750 ml of fresh frozen plasma brought it to mid-normal (1'45"). The surgical procedure proved uneventful, with minimal bleeding, the lesion proving to be a benign hemangioma. The boy went home on the second postoperative day.

Case 3—Warfarin toxicity

A 45-year-old woman entered the hospital for extraction of 16 teeth. The oral surgeon called in a physician consultant, who failed to elicit

*Courtesy of Judith B. Pool, Ph.D., Coagulation Laboratory, Stanford University School of Medicine, Stanford.

**Courtesy of Sylvija Hoag, M.D., Hematology Research Laboratory, Children's Hospital of San Francisco.

any story of abnormal bleeding. We found the routine preoperative ACT definitely prolonged, however (3'45", 3'40"), the bleeding time, platelets and clot retraction normal. On our recommendation, the oral surgeon delayed his procedure for further investigation.

Further study demonstrated prolongation of the Quick prothrombin time (30" = 15 percent; control: 13"), of the P & P test (58" = less than 10 percent; control: 22"), and of the activated PTT (80").

More careful clinical history revealed that this patient with chronic rheumatic heart disease had undergone an open heart operation a year before for placement of a prosthetic aortic valve. She had received sodium warfarin since, recently taking 10 mg and 12.5 mg on alternate days. She had not mentioned anti-coagulant therapy to her questioner, who had not asked her specifically about it.

In preparation for operation, the patient received two injections of vitamin K-1 oxide, 10 mg each. Within two days the prothrombin activity had risen into the safe range for an operative procedure (Quick: 15.2 sec = 62 percent; P & P: 26 sec = 70 percent). The extractions went smoothly, without excessive bleeding, and the patient recovered without difficulty. She subsequently again received sodium warfarin.

Discussion

Our experience with these three patients, and with many others like them, has confirmed our conviction that taking a patient to surgery without laboratory screening for coagulation defects poses definite risks. The patient may be confused or disoriented (as in Case 1 reported herein) or he may be ignorant of the facts. The person supplying the history may be unwilling to disclose the facts (as in Case 2). Some small children with hemostatic disorders have never bled abnormally simply because they have never met sufficient hemostatic challenge to bring their bleeding tendency to light. Finally (as in Case 3) even astute physicians sometimes do not take a complete history. Hence the history alone may at times fail to detect important hemostatic defects.

After many thousands of determinations in our laboratories, the activated coagulation time of whole blood (ACT) has in our opinion thoroughly established its usefulness. When performed at 37° C as described, this simple bedside test has proven comparable in sensitivity to the activated PTT. We feel that one or the other of these two tests belongs in every routine preoperative work-up, along with a careful history. We also urge use of a sensitive bleeding time determination, screening of the smear for platelets, and observation of the incubated clot for clot retraction and fibrinolysis.

REFERENCES

1. Hattersley PG: Activated coagulation time of whole blood. JAMA 196:436-440, 1966
2. Hattersley PG: The treatment of classical hemophilia with cryoprecipitates. JAMA 198: 243-247, 1966
3. Djerassi I: Personal communication, 1968
4. Brittin GM: Personal communication, 1968
5. Hattersley PG, Hayse D: Fletcher factor deficiency: A report of three unrelated cases. Brit J Haemat. In press
6. Hattersley PG, Dimick ML: Cryoprecipitates in treatment of congenital fibrinogen deficiency. Transfusion 9:261-264, Sept-Oct, 1969
7. Miale JB: Laboratory Medicine: Hematology, 3rd ed. St. Louis, CV Mosby Co, 1967
8. Quick AJ: Hemorrhagic Diseases and Thrombosis, 2nd ed. Philadelphia, Lea and Febiger, 1966
9. Ware AG, Stragnell R: An improved one-stage prothrombin method. Amer J Clin Path 22:791-797, 1952
10. Hardisty RM, Ingram GIC: Bleeding Disorders: Investigation and Management. Philadelphia, FA Davis Co, 1966
11. Cullen GE, Van Slyke DD: Determination of fibrinogen, globulin and albumin nitrogen of blood plasma. J Biol Chem 41:587, 1920
12. Proctor RR, Rapaport SI: The partial thromboplastin time with kaolin. Amer J Clin Path 36:212-219, 1961
13. Pool JB, Shannon AE: Simple production of high-potency antihemophilic globulin concentrates (AHG) in closed bag system. Fed Proc 24:512, 1965
14. Pool JG, Shannon AE: Production of high-potency concentrates of antihemophilic globulin in a closed bag system. New Eng J Med 273:1443-1447, 1965